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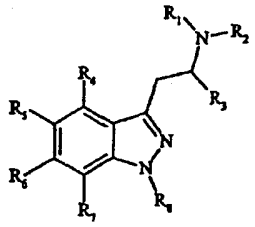

(I)

(57) Abstract

For use in therapy, a chemical compound of formula (I) wherein R_1 and R_2 are independently selected from hydrogen and alkyl; R_3 is alkyl; R_4 to R_7 are independently selected from hydrogen, halogen, hydroxy, alkyl, aryl, amino, monoalkylamino, dialkylamino, alkoxy, aryloxy, alkylthio, arylthio, arylsulfoxyl, arylsulfonyl, alkylsulfoxyl, alkylsulfonyl, nitro, cyano, carboxaldehyde, alkylcarbonyl, arylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkoxycarbonylamino, aminocarbonyloxy, monoalkylaminocarbonyloxy, dialkylaminocarbonyloxy, monoalkylaminocarbonylamino and dialkylaminocarbonylamino, wherein at least one of R_4 to R_7 is a substituent group other than hydrogen; and R_8 is selected from hydrogen and alkyl, and pharmaceutically acceptable salts and prodrugs thereof, other than compounds in which R_1 is hydrogen and R_2 is $-CH_2CH(OH)-Ar$ and other than compounds in which R_2 is H and R_1 is $-CH_2CH(OH)-Ar$ wherein Ar is 3–halophenyl or 3–trifluoromethylphenyl, and the use thereof in therapy, particularly for the treatment of disorders of the central nervous system; damage to the central nervous system; cardiovascular disorders; gastrointestinal disorders; diabetes insipidus, and sleep apnea, and particularly for the treatment of obesity; novel chemical compounds of formula (I).

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CHEMICAL COMPOUNDS III

The present invention relates to indazole derivatives, to processes and intermediates for their preparation, to pharmaceutical compositions containing them and to their medicinal use. The active compounds of the present invention are useful in treating obesity and other disorders.

It has been recognised that obesity is a disease process influenced by environmental factors in which the traditional weight loss methods of dieting and exercise need to be supplemented by therapeutic products (S. Parker, *"Obesity: Trends and Treatments"*, Scrip Reports, PJB Publications Ltd, 1996).

Whether someone is classified as overweight or obese is generally determined on the basis of their body mass index (BMI) which is calculated by dividing body weight (kg) by height squared (m^2). Thus, the units of BMI are kg/m^2 and it is possible to calculate the BMI range associated with minimum mortality in each decade of life. Overweight is defined as a BMI in the range 25-30 kg/m^2, and obesity as a BMI greater than 30 kg/m^2. There are problems with this definition in that it does not take into account the proportion of body mass that is muscle in relation to fat (adipose tissue). To account for this, obesity can also be defined on the basis of body fat content: greater than 25% and 30% in males and females, respectively.

As the BMI increases there is an increased risk of death from a variety of causes that is independent of other risk factors. The most common diseases with obesity are cardiovascular disease (particularly hypertension), diabetes (obesity aggravates the development of diabetes), gall bladder disease (particularly cancer) and diseases of reproduction. Research has shown that even a modest reduction in body weight can correspond to a significant reduction in the risk of developing coronary heart disease.

Compounds marketed as anti-obesity agents include Orlistat (Reductil®) and Sibutramine. Orlistat (a lipase inhibitor) inhibits fat absorption directly and tends to produce a high incidence of unpleasant (though relatively harmless) side-effects such as diarrhoea. Sibutramine (a mixed 5-HT/noradrenaline reuptake inhibitor) can increase

blood pressure and heart rate in some patients. The serotonin releaser/reuptake inhibitors fenfluramine (Pondimin®) and dexfenfluramine (Redux™) have been reported to decrease food intake and body weight over a prolonged period (greater than 6 months). However, both products were withdrawn after reports of preliminary evidence of heart valve abnormalities associated with their use. There is therefore a need for the development of a safer anti-obesity agent.

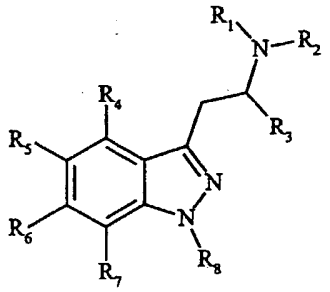
The non-selective 5-HT_{2C} receptor agonists/partial agonists m-chlorophenylpiperazine (mCPP) and trifluoromethylphenylpiperazine (TFMPP) have been shown to reduce food intake in rats (G.A. Kennett and G. Curzon, *Psychopharmacol.*, 1988, **96**, 93-100; G.A. Kennett, C.T. Dourish and G. Curzon, *Eur. J. Pharmacol.*, 1987, **141**, 429-435) and to accelerate the appearance of the behavioural satiety sequence (S.J. Kitchener and C.T. Dourish, *Psychopharmacol.*, 1994, **113**, 369-377). Recent findings from studies with mCPP in normal human volunteers and obese subjects have also shown decreases in food intake. Thus, a single dose of mCPP decreased food intake in female volunteers (A.E.S. Walsh *et al.*, *Psychopharmacol.*, 1994, **116**, 120-122) and decreased the appetite and body weight of obese male and female subjects during subchronic treatment for a 14 day period (P.A. Sargeant *et al.*, *Psychopharmacol.*, 1997, **133**, 309-312). The anorectic action of mCPP is absent in 5-HT_{2C} receptor knockout mutant mice (L.H. Tecott *et al.*, *Nature*, 1995, **374**, 542-546) and is antagonised by the 5-HT_{2C} receptor antagonist SB-242084 in rats (G.A. Kennett *et al.*, *Neuropharmacol.*, 1997, **36**, 609-620). It seems therefore that mCPP decreases food intake via an agonist action at the 5-HT_{2C} receptor.

Other compounds which have been proposed as 5-HT_{2C} receptor agonists for use in the treatment of obesity include the substituted 1-aminoethyl indoles disclosed in EP-A-0655440. CA-2132887 and CA-2153937 disclose that tricyclic 1-aminoethylpyrrole derivatives and tricyclic 1-aminoethyl pyrazole derivatives bind to 5-HT_{2C} receptors and may be used in the treatment of obesity. WO-A-98/30548 discloses aminoalkylindazole compounds as 5-HT_{2C} agonists for the treatment of CNS diseases and appetite regulation disorders. EP-A-0494774 discloses 5-[(oxadiazolyl)alkyl]- and 5-[(thiadiazolyl)alkyl]-1H-indazole-3-ethanamines and their use as 5-HT_1 receptor agonists (selective vasoconstrictors). The synthesis and radioprotective activity of β–(3-

indazolyl)ethylamine derivatives have been disclosed by E. Rao *et al. Yaoxue Xuebao*, 1987, **22(6)**, 426). JP-A-08/165276 discloses 2-[2-(indazol-3-yl)-ethyl]amino-1-phenylethanol derivatives as β_3 receptor ligands.

It is an object of this invention to provide selective, directly acting $5HT_2$ receptor ligands for use in therapy and particularly for use as anti-obesity agents. It is a further object of this invention to provide directly acting ligands selective for 5-HT_{2B} and/or 5-HT_{2C} receptors, for use in therapy and particularly for use as anti-obesity agents. It is a further object of this invention to provide selective, directly acting 5-HT_{2C} receptor ligands, preferably 5-HT_{2C} receptor agonists, for use in therapy and particularly for use as anti-obesity agents.

According to the present invention there is provided, for use in therapy, a chemical compound of formula (I):



(I)

wherein:

R_1 and R_2 are independently selected from hydrogen and alkyl;

R_3 is alkyl;

R_4 to R_7 are independently selected from hydrogen, halogen, hydroxy, alkyl, aryl, amino, monoalkylamino, dialkylamino, alkoxy, aryloxy, alkylthio, arylthio, arylsulfoxyl, arysulfonyl, alkylsulfoxyl, alkylsulfonyl, nitro, cyano, carboxaldehyde, alkylcarbonyl, arylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkoxycarbonylamino, aminocarbonyloxy, monoalkylaminocarbonyloxy, dialkylaminocarbonyloxy, monoalkylaminocarbonylamino and dialkylaminocarbonylamino, wherein at least one of R_4 to R_7 is a substituent group other than hydrogen; and

R_8 is selected from hydrogen and alkyl,

and pharmaceutically acceptable salts and prodrugs thereof,

other than compounds in which R_1 is hydrogen and R_2 is $-CH_2CH(OH)$-Ar and other than compounds in which R_2 is H and R_1 is $-CH_2CH(OH)$-Ar wherein Ar is 3-halophenyl or 3-trifluoromethylphenyl.

As used herein, the term "alkyl" means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical. Where cyclic, the alkyl group is preferably C_3 to C_{12}, more preferably C_5 to C_{10}, more preferably C_5, C_6 or C_7. Where acyclic, the alkyl group is preferably C_1 to C_{10}, more preferably C_1 to C_6, more preferably methyl, ethyl, propyl (n-propyl or isopropyl) or butyl (n-butyl, isobutyl or tertiary butyl), more preferably methyl.

As used herein, the term "lower alkyl" means methyl, ethyl, propyl (n-propyl or isopropyl) or butyl (n-butyl, isobutyl or tertiary butyl).

As used herein, the term "aryl" means an aromatic group, such as phenyl or naphthyl, or a heteroaromatic group containing one or more, preferably one, heteratom, such as pyridyl, pyrrolyl, furanyl and thienyl.

The alkyl and aryl groups may be substituted or unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 substituent. Substituents may include:

carbon-containing groups such as

- alkyl,
- aryl,
- arylalkyl (e.g. substituted and unsubstituted phenyl, substituted and unsubstituted benzyl);

halogen atoms and halogen-containing groups such as

- haloalkyl (e.g. trifluoromethyl);

oxygen-containing groups such as

- alcohols (e.g. hydroxy, hydroxyalkyl, aryl(hydroxy)alkyl),
- ethers (e.g. alkoxy, aryloxy, alkoxyalkyl, aryloxyalkyl),

aldehydes (e.g. carboxaldehyde),
ketones (e.g. alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylalkylcarbonyl, arylcarbonylalkyl),
acids (e.g. carboxy, carboxyalkyl),
acid derivatives such as esters (e.g. alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl),
amides (e.g. aminocarbonyl, mono- or di-alkylaminocarbonyl, aminocarbonylalkyl, mono- or di-alkylaminocarbonylalkyl, arylaminocarbonyl),
carbamates (e.g. alkoxycarbonylamino, aryloxycarbonylamino, aminocarbonyloxy, mono- or di-alkylaminocarbonyloxy, arylaminocarbonyloxy)
and ureas (e.g. mono- or di-alkylaminocarbonylamino or arylaminocarbonylamino);

nitrogen-containing groups such as
amines (e.g. amino, mono- or di-alkylamino, aminoalkyl, mono- or di-alkylaminoalkyl),
azides,
nitriles (e.g. cyano, cyanoalkyl),
nitro;

sulfur-containing groups such as
thiols, thioethers, sulfoxides and sulfones (e.g. alkylthio, alkylsulfinyl, alkylsulfonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, arylthio, arylsulfinyl, arylsulfonyl, arylthioalkyl, arylsulfinylalkyl, arylsulfonylalkyl);

and heterocyclic groups containing one or more, preferably one, heteroatom,

(e.g. thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, aziridinyl, azetidinyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, hexahydroazepinyl, piperazinyl, morpholinyl, thianaphthyl, benzofuranyl, isobenzofuranyl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolinyl, isoquinolinyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxalinyl, chromenyl, chromanyl, isochromanyl, phthalazinyl and carbolinyl).

As used herein, the term "alkoxy" means alkyl-O- and "alkoyl" means alkyl-CO-. Alkoxy substituent groups or alkoxy-containing substituent groups may be substituted by one or more alkyl groups.

As used herein, the term "halogen" means a fluorine, chlorine, bromine or iodine radical, preferably a fluorine, chlorine or bromine radical.

As used herein the term "prodrug" means any pharmaceutically acceptable prodrug of the compound of formula (I).

As used herein, the term "pharmaceutically acceptable salt" means any pharmaceutically acceptable salt of the compound of formula (I). Salts may be prepared from pharmaceutically acceptable non-toxic acids and bases including inorganic and organic acids and bases. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, dichloroacetic, formic, fumaric, gluconic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, oxalic, pamoic, pantothenic, phosphoric, succinic, sulfuric,

tartaric, oxalic, p-toluenesulfonic and the like. Particularly preferred are fumaric, hydrochloric, hydrobromic, phosphoric, succinic, sulfuric and methanesulfonic acids. Acceptable base salts include alkali metal (e.g. sodium, potassium), alkaline earth metal (e.g. calcium, magnesium) and aluminium salts.

In a preferred embodiment of the present invention, R_1 and R_2 are independently selected from hydrogen and lower alkyl.

Preferably, the compounds of formula (I) are selected from compounds in which R_1 is the same as R_2. Preferably, R_1 and R_2 are both hydrogen. In an embodiment of the present invention, R_1 is hydrogen and R_2 is alkyl, preferably lower alkyl, preferably methyl.

Preferably, the compounds of formula (I) are selected from compounds in which R_3 is selected from alkyl other than ethyl. Most preferably R_3 is methyl. The carbon atom to which R_3 is attached is an asymmetric carbon atom. It is preferred that this asymmetric carbon atom is in the (*S*)-configuration, wherein the stereochemical assignment is defined with respect to a compound wherein R_3 is an unsubstituted alkyl group.

R_4 to R_7 are independently selected from hydrogen, halogen, hydroxy, alkyl (including cycloalkyl, halo-alkyl (such as trifluoromethyl) and arylalkyl), aryl, amino, monoalkylamino, dialkylamino, alkoxy (including arylalkoxy), aryloxy, alkylthio, arylthio, arysulfoxyl, arylsulfonyl, alkylsulfoxyl, alkylsulfonyl, nitro, cyano, carboxaldehyde, alkylcarbonyl, arylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkoxycarbonylamino, aminocarbonyloxy, monoalkylaminocarbonyloxy, dialkylaminocarbonyloxy, monoalkylaminocarbonylamino and dialkylaminocarbonylamino, wherein at least one of R_4 to R_7 is a substituent group other than hydrogen.

In one embodiment, R_4 to R_7 are independently selected from hydrogen, halogen, hydroxy, alkyl (including cycloalkyl, halo-alkyl (such as trifluoromethyl) and arylalkyl), aryl, alkoxy (including arylalkoxy), aryloxy, alkylthio, alkylsulfoxyl and

alkylsulfonyl, wherein at least one of R_4 to R_7 is a substituent group other than hydrogen.

Preferably, the compounds of formula (I) are selected from compounds in which two or three of R_4, R_5, R_6 and R_7 are hydrogen. Preferably, one or both of R_4 and R_7 are hydrogen. Preferably one or both of R_5 and R_6, preferably at least R_5, is selected from alkyl (preferably lower alkyl and preferably trifluoromethyl), alkoxy (preferably lower alkoxy and more preferably methoxy), halogen and alkylthio (preferably lower alkylthio). In an alternative embodiment, R_6 is selected from hydrogen and halogen, and preferably from hydrogen and fluoro. In a further alternative embodiment, R_5 is selected from alkyl (preferably lower alkyl and preferably trifluoromethyl), alkoxy (preferably lower alkoxy and more preferably methoxy), halogen (preferably chloro and bromo) and alkylthio (preferably lower alkylthio).

In the compounds of formula (I) wherein R_8 is selected from alkyl, it is preferred that R_8 is selected from lower alkyl, preferably methyl. Preferably R_8 is hydrogen.

In a preferred embodiment, the compounds of formula (I) are selected from 1-(5-chloroindazol-3-yl)-2-propylamine, 1-(5-chloro-1-methylindazol-3-yl)-2-propylamine, 1-(5-chloro-1-isopropylindazol-3-yl)-2-propylamine, 1-(5-methoxyindazol-3-yl)-2-propylamine, 1-(5-methoxy-1-methylindazol-3-yl)-2-propylamine and 1-(5-bromoindazol-3-yl)-2-propylamine, preferably the (*S*)-enantiomers thereof. Where the compounds of formula (I) are in the form of a salt, the fumarate salt is preferred.

In an alternative embodiment, the compounds of formula (I) are selected from 1-(5-chloro-1-methylindazol-3-yl)-2-propylamine, 1-(5-chloro-1-isopropylindazol-3-yl)-2-propylamine, 1-(5-methoxyindazol-3-yl)-2-propylamine, 1-(5-methoxy-1-methylindazol-3-yl)-2-propylamine and 1-(5-bromoindazol-3-yl)-2-propylamine, and preferably the (*S*)-enantiomers thereof. Where the compounds of formula (I) are in the form of a salt, the fumarate salt is preferred.

1-(5-Bromoindazol-3-yl)-2-propylamine, 1-(5-chloroindazol-3-yl)-2-propylamine and 1-(5-methoxyindazol-3-yl)-2-propylamine are particularly preferred.

The compounds of formula (I) may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. The compounds can be, for example, racemates or optically active forms. The optically active forms can be obtained by resolution of the racemates or by asymmetric synthesis.

In a preferred embodiment of the invention, a compound of formula (I) is in the form of its (*S*)-enantiomer, substantially free of its (*R*)-enantiomer. As used herein, the term "substantially free of its (*R*)-enantiomer" means that a composition comprising a compound of formula (I) contains a greater proportion of the (*S*)-enantiomer of the compound of formula (I) in relation to the (*R*)-enantiomer of the compound of formula (I). In a preferred embodiment of the present invention, the term "substantially free of its (*R*)-enantiomer", as used herein, means that the composition contains at least 90 % by weight of the (*S*)-enantiomer and 10 % by weight or less of the (*R*)-enantiomer. In a further preferred embodiment, the term "substantially free of its (*R*)-enantiomer" means that the composition contains at least 99 % by weight of the (*S*)-enantiomer and 1 % or less of the (*R*)-enantiomer. In another preferred embodiment, the term "substantially free of its (*R*)-enantiomer" means that the composition contains 100 % by weight of the (*S*)-enantiomer. The above percentages are based on the total amount of a compound of formula (I) present in the composition.

According to a further aspect of the invention, there is provided a novel compound of formula (I), *per se*. In an embodiment of the invention, there is provided a compound of formula (I), *per se*, wherein at least one of R_4 to R_8, preferably at least one of R_5 and R_6, is a substituent other than alkyl, preferably other than methyl. In a further embodiment of the invention, there is provided a compound of formula (I), *per se*, wherein at least one of R_4 to R_7, preferably at least one of R_5 and R_6 is a substituent other than halogen, preferably other than chloro, or a substituent other than alkoxy, preferably other than methoxy.

In a further embodiment of the present invention, there is provided a compound of formula (I), *per se*, wherein R_4 to R_7 are selected from hydrogen, fluorine, bromine, hydroxy, aryl, amino, monoalkylamino, dialkylamino, aryloxy, alkylthio, arylthio

arylsulfoxyl, arylsulfonyl, alkylsulfoxyl, alkylsulfonyl, nitro, cyano, carboxaldehyde, alkylcarbonyl, arylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkoxycarbonylamino, aminocarbonyloxy, monoalkylaminocarbonyloxy, dialkylaminocarbonyloxy, monoalkylaminocarbonylamino and dialkylaminocarbonylamino, wherein at least one of R_4 to R_7 is a substituent other than hydrogen.

In a further embodiment of the present invention, there is provided a compound of formula (I), *per se*, wherein R_4 to R_7 are selected from hydrogen, hydroxy, aryl, amino, monoalkylamino, dialkylamino, aryloxy, alkylthio, arylthio, arylsulfoxyl, arylsulfonyl, alkylsulfoxyl, alkylsulfonyl, nitro, cyano, carboxaldehyde, alkylcarbonyl, arylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkoxycarbonylamino, aminocarbonyloxy, monoalkylaminocarbonyloxy, dialkylaminocarbonyloxy, monoalkylaminocarbonylamino and dialkylaminocarbonylamino, wherein at least one of R_4 to R_7 is a substituent other than hydrogen.

The compounds of formula (I) may be used in the treatment (including prophylactic treatment) of disorders associated with 5-HT_2 receptor function. The compounds may act as receptor agonists or antagonists. Preferably, the compounds may be used in the treatment (including prophylactic treatment) of disorders associated with 5-HT_{2B} and/or 5-HT_{2C} receptor function. Preferably, the compounds may be used in the treatment (including prophylactic treatment) of disorders where a 5-HT_{2C} receptor agonist is required.

The compounds of formula (I) may be used in the treatment or prevention of central nervous disorders such as depression, atypical depression, bipolar disorders, anxiety disorders, obsessive-compulsive disorders, social phobias or panic states, sleep disorders, sexual dysfunction, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or other pain, raised intracranial pressure, epilepsy, personality disorders, age-related behavioural disorders, behavioural disorders associated with dementia, organic mental disorders, mental disorders in childhood, aggressivity, age-related memory disorders, chronic fatigue syndrome, drug and alcohol

addiction, obesity, bulimia, anorexia nervosa or premenstrual tension; damage of the central nervous system such as by trauma, stroke, neurodegenerative diseases or toxic or infective CNS diseases such as encephalitis or meningitis; cardiovascular disorders such as thrombosis; gastrointestinal disorders such as dysfunction of gastrointestinal motility; diabetes insipidus; and sleep apnea.

According to a further aspect of the invention, there is provided use of a compound of formula (I) in the manufacture of a medicament for the treatment (including prophylaxis) of the above-mentioned disorders. In a preferred embodiment, there is provided use of a compound of formula (I) in the manufacture of a medicament for the treatment (including prophylaxis) of obesity.

According to a further aspect of the invention, there is provided a method of treatment (including prophylaxis) of a disorder selected from the group consisting of the above-mentioned disorders comprising administering to a patient in need of such treatment an effective dose of a compound of formula (I). In a preferred embodiment, there is provided a method of treatment (including prophylaxis) of obesity.

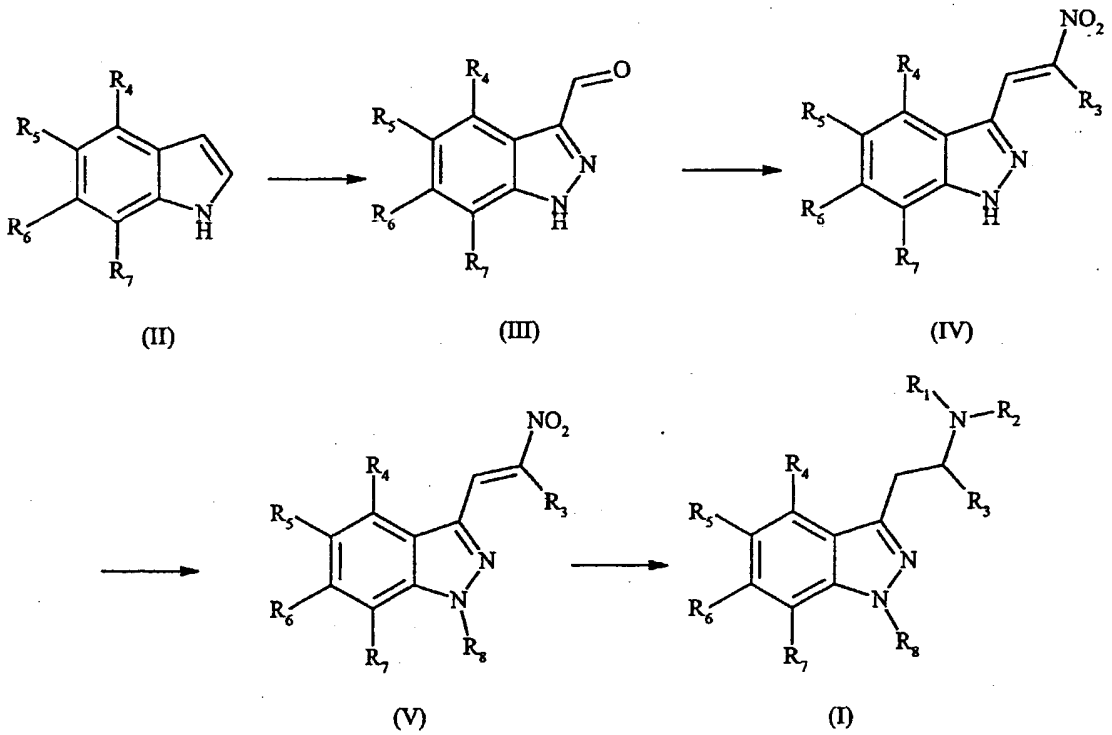
According to a further aspect of the invention, there is provided a pharmaceutical composition comprising a compound of formula (I) in combination with a pharmaceutically acceptable carrier or excipient and a method of making such a composition comprising combining a compound of formula (I) with a pharmaceutically acceptable carrier or excipient.

According to a further aspect of the invention, there is provided a method of preparing a compound of formula (I).

Compounds of formula (I) may be prepared according to Reaction Scheme 1 below. R_1 to R_8 are as previously defined. The indazole-3-carboxaldehyde (III) may be prepared by reaction of indole (II) with acidic aqueous sodium nitrite solution. The 1-(indazol-3-yl)-2-nitropropene (V) can be formed in a two step procedure from the aldehyde (III) by reaction with a nitro alkane in the presence of ammonium acetate, followed by protection at nitrogen. Reduction of the nitroalkene (V) to a compound of

formula (I) (R_1 = R_2 = H) may be achieved using lithium aluminium hydride in a suitable solvent such as tetrahydrofuran.

Reaction Scheme 1



The compounds of formula (I) (R_1 and/or R_2 = alkyl) may be prepared from compounds of formula (I) (R_1 = R_2 = H) by standard methods such as reductive alkylation with an appropriate aldehyde or ketone in the presence of a reducing agent such as sodium triacetoxyborohydride, formic acid or sodium cyanoborohydride.

If, in any of the processes mentioned herein, the substituent group R_4, R_5, R_6, R_7 or R_8 is other than the one required, the substituent group may be converted to the desired substituent by known methods. The substituents R_4, R_5, R_6, R_7 or R_8 may also need protecting against the conditions under which the reaction is carried out. In such a case, the protecting group may be removed after the reaction has been completed.

The processes described above may be carried out to give a compound of formula (I) in the form of a free base or as an acid addition salt. If the compound of the

invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid addition salt. Conversely, if the product of the process is a free base, an acid addition salt, particularly a pharmaceutically acceptable acid addition salt, may be obtained by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from basic compounds.

The compositions comprising a compound of formula (I) may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds of formula (I) may be formulated for oral, buccal, intranasal, parenteral (*e.g.*, intravenous, intramuscular or subcutaneous) transdermal or rectal administration or in a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (*e.g.* pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropylmethylcellulose); fillers (*e.g.* lactose, microcrystalline cellulose or calcium phosphate); lubricants (*e.g.* magnesium stearate, talc or silica); disintegrants (*e.g.* potato starch or sodium starch glycollate); or wetting agents (*e.g.* sodium lauryl sulfate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (*e.g.* sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (*e.g.* lecithin or acacia); non-aqueous vehicles (*e.g.* almond oil, oily esters or ethyl alcohol); and preservatives (*e.g.* methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The active compounds of formula (I) may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents.

Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, *e.g.* sterile pyrogen-free water, before use.

The active compounds of formula (I) may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds of formula (I) are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, *e.g.* dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

A proposed dose of the active compounds of formula (I) for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above (*e.g.*, obesity) is 0.1 to 500 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

The invention will now be described in detail with reference to the following examples. It will be appreciated that the invention is described by way of example only and modification of detail may be made without departing from the scope of the invention.

EXPERIMENTAL

Assay Procedure for Functional activity

The functional activity of compounds of formula (I) was assayed using a Fluorimetric Imaging Plate reader (FLIPR). CHO cells expressing the human 5-HT_{2C} or human 5-HT_{2A} receptors were counted and plated into standard 96 well microtitre plates on the day before testing to give a confluent monolayer. The cells were then dye loaded with the calcium sensitive dye, Fluo-3-AM. Unincorporated dye was removed using an automated cell washer to leave a total volume of 100 µL/well of assay buffer (Hanks balanced salt solution containing 20 mM Hepes and 2.5 mM probenecid). The drug (dissolved in 50 µL of the assay buffer) was added at a rate of 70 µL/sec to each well of the FLIPR 96 well plate during fluorescence measurements. The measurements were taken at 1 sec intervals and the maximum fluorescent signal was measured (approx 10-15 secs after drug addition) and compared with the response produced by 10 µM 5-HT (defined as 100%) to which it was expressed as a percentage response (relative efficacy). Dose response curves were constructed using Graphpad Prism (Graph Software Inc.).

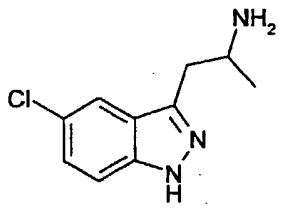
The thus determined activity of compounds of formula (I) is shown in Table 1.

Table 1

Compound	h5-HT_{2A}		h5-HT_{2C}	
	EC_{50} (nM)	Relative Efficacy (%)	EC_{50} (nM)	Relative Efficacy (%)
Example 1	346	46	55	51
Example 6	415	53	159	62

Synthetic Examples

Example 1: (*RS*)-1-(5-Chloroindazol-3-yl)-2-propylamine fumarate



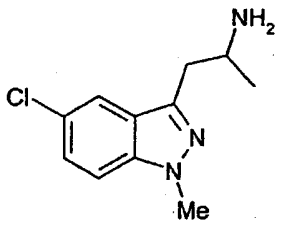
1-(5-Chloroindazol-3-yl)-2-nitropropene

To 5-chloroindazole-3-carboxaldehyde (*J. Am. Chem. Soc.*, 1986, **108**, 4115-4119) (0.42 g, 2.33 mmol) was added ammonium acetate (0.18 g, 2.33 mmol) and nitroethane (10 mL) and the reaction mixture was heated at 100°C for 1 h. After cooling to room temperature, the reaction mixture was poured into water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with saturated brine (100 mL), dried (magnesium sulfate), concentrated *in vacuo* and purified by column chromatography [SiO_2; heptane-ethyl acetate (2 : 1)] to yield 1-(5-chloroindazol-3-yl)-2-nitropropene (0.18 g, 33%) as a yellow solid: mp 208-209 °C; IR ν_{max}(Nujol)/cm^{-1} 3388, 2854, 1650, 1510 and 1298; NMR δ_H (400 MHz, DMSO-d_6) 2.74 (3H, s), 7.46 (1H, dd, *J* 2.0, 7.0 Hz), 7.69 (1H, d, *J* 7.0 Hz), 8.30 (1H, d, *J* 2.0 Hz), 8.40 (1H, s) and 14.10 (1H, br s).

(*RS*)-1-(5-Chloroindazol-3-yl)-2-propylamine fumarate

To lithium aluminium hydride (0.12 g, 3.20 mmol) in anhydrous tetrahydrofuran (5 mL) was added dropwise a solution of 1-(5-chloroindazol-3-yl)-2-nitropropene (0.38 g, 1.60 mmol) in anhydrous tetrahydrofuran (5 mL). The reaction mixture was heated under reflux for 3 h. After cooling to room temperature, ether (25 mL) was added followed by saturated aqueous sodium sulfate solution (2 mL). The reaction mixture was filtered through a pad of kieselguhr and the filtrate was concentrated *in vacuo* to yield a yellow-brown oil. The oil (0.058 g, 0.28 mmol) was dissolved in ether (5 mL) and fumaric acid (0.033 g, 0.28 mmol) in 2-propanol (5 mL) was added. A precipitate formed which was dissolved in 2-propanol at 50 °C. The solution was cooled to 0 °C and filtered. The filter-cake was dried *in vacuo* to yield the product (0.085 g, 16%) as an off-white solid: mp 201 °C; IR ν_{max}(Nujol)/cm^{-1} 1688, 1609, 1567 and 1526; NMR δ_H (400 MHz, DMSO-d_6) 1.16 (3H, d, *J* 6.6 Hz), 3.05 (1H, dd, *J* 8.7, 14.8 Hz), 3.24 (1H, dd, *J* 5.5, 14.7 Hz), 3.53 (1H, m), 6.44 (2H, s), 7.34 (1H, dd, *J* 2.0, 7.0 Hz), 7.54 (1H, d, *J* 7.5 Hz) and 7.92 (1H, d, *J* 1.8 Hz); Found: C, 52.40; H, 5.12; N, 13.83%. $C_{10}H_{12}N_3Cl.0.8C_4H_4O_4$ requires: C, 52.40; H, 5.06; N, 13.89%.

Example 2: (*RS*)-1-(5-Chloro-1-methylindazol-3-yl)-2-propylamine fumarate



1-(5-Chloro-1-methylindazol-3-yl)-2-nitropropene

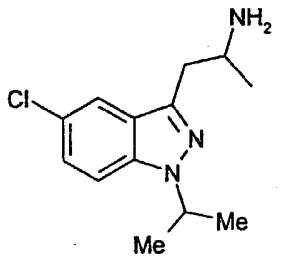
To a stirred suspension of powdered potassium hydroxide (0.22 g, 3.18 mmol) in methyl sulfoxide (10 mL) at 10°C was added a solution of 1-(5-chloroindazol-3-yl)-2-nitropropene (0.63 g, 2.65 mmol) in methyl sulfoxide (5 mL). The reaction mixture was stirred for 30 min and then iodomethane (0.45 g, 3.18 mmol) was added. The reaction mixture was warmed to room temperature, stirred for 2 h, poured into ice-water (200 mL) and filtered. The filter-cake was washed with ice-water (50 mL) and dried *in vacuo* to yield 1-(5-chloro-1-methylindazol-3-yl)-2-nitropropene (0.57 g, 85%) as a

yellow solid: mp 187-189 °C; IR ν_{max}(Nujol)/cm^{-1} 1730, 1654, 1551 and 1512; NMR δ_H (400 MHz, $CDCl_3$) 2.79 (3H, s), 4.16 (3H, s), 7.41 (2H, m), 7.82 (1H, m) and 8.21 (1H, s).

(*RS*)-1-(5-Chloro-1-methylindazol-3-yl)-2-propylamine fumarate

(*RS*)-1-(5-Chloro-1-methylindazol-3-yl)-2-propylamine fumarate was prepared according to the method described in Example 1 using 1-(5-chloro-1-methylindazol-3-yl)-2-nitropropene to give 0.16 g (28%) of the product as an off-white solid: mp 146-147 °C; IR ν_{max}(Nujol)/cm^{-1} 1692, 1640 and 1510; NMR δ_H (400 MHz, DMSO-d_6) 1.18 (3H, d, *J* 6.5 Hz), 3.05 (1H, dd, *J* 8.3, 14.4 Hz), 3.24 (1H, dd, *J* 5.8, 14.4 Hz), 3.56 (1H, m), 4.01 (3H, s), 6.45 (2H, s), 7.41 (1H, dd, *J* 2.0, 7.0 Hz), 7.66 (1H, d, *J* 7.5 Hz) and 7.93 (1H, d, *J* 2.0 Hz).

Example 3: (*RS*)-1-(5-Chloro-1-isopropylindazol-3-yl)-2-propylamine fumarate



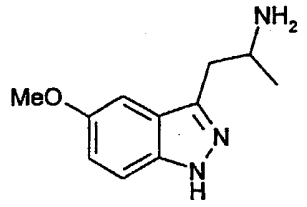
1-(5-Chloro-1-isopropylindazol-3-yl)-2-nitropropene

1-(5-Chloro-1-isopropylindazol-3-yl)-2-nitropropene was prepared according to the method described in Example 2 using 1-(5-chloroindazol-3-yl)-2-nitropropene to give 0.27 g (31%) of the product as a yellow solid: mp 159-160 °C; IR ν_{max}(Nujol)/cm^{-1} 1655, 1612, 1567, 1549, 1510 and 1215; NMR δ_H (400 MHz, $CDCl_3$) 1.63 (6H, d, *J* 6.4 Hz), 2.81 (3H, s), 4.89 (1H, septet, *J* 6.5 Hz), 7.41 (2H, m), 7.82 (1H, m) and 8.23 (1H, s).

(*RS*)-1-(5-Chloro-1-isopropylindazol-3-yl)-2-propylamine fumarate

(*RS*)-1-(5-Chloro-1-isopropylindazol-3-yl)-2-propylamine fumarate was prepared according to the method described in Example 1 using 1-(5-chloro-1-isopropylindazol-3-yl)-2-nitropropene to give 0.057 g (16%) of the product as a white solid: mp 140 °C; IR ν_{max}(Nujol)/cm^{-1} 1701, 1629 and 1499; NMR δ_H (400 MHz, DMSO-d_6) 1.16 (3H, d, *J* 6.6 Hz), 1.45 (6H, d, *J* 6.5 Hz), 3.05 (1H, dd, *J* 8.3, 14.4 Hz), 3.25 (1H, dd, *J* 5.2, 14.4 Hz), 3.54 (1H, m), 4.95 (1H, septet, *J* 6.5 Hz), 6.44 (2H, s), 7.38 (1H, dd, *J* 2.0, 7.0 Hz), 7.72 (1H, d, *J* 7.5 Hz) and 7.92 (1H, d, *J* 2.0 Hz); Found: C, 54.95; H, 5.94; N, 10.90%. $C_{13}H_{18}N_3Cl.1.15C_4H_4O_4$ requires: C, 54.87; H, 5.91; N, 10.91%.

Example 4: (*RS*)-1-(5-Methoxyindazol-3-yl)-2-propylamine fumarate



1-(5-Methoxyindazol-3-yl)-2-nitropropene

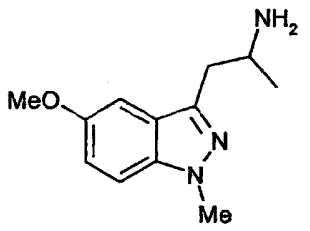
1-(5-Methoxyindazol-3-yl)-2-nitropropene was prepared according to the method described in Example 1 using 5-methoxyindazole-3-carboxaldehyde (*J. Med. Chem.* 1995, **38**(13), 2331-8) to give 0.14 g (17%) of the product as a yellow solid: mp 194 °C; IR ν_{max}(Nujol)/cm^{-1} 3172, 1651, 1630, 1509 and 1323; NMR δ_H (400 MHz, DMSO-d_6) 2.76 (3H, s), 3.86 (3H, s), 7.10 (1H, dd, *J* 2.5, 9.0 Hz), 7.55 (1H, d, *J* 9.0 Hz), 7.57 (1H, d, *J* 2.0 Hz), 8.42 (1H, s) and 13.83 (1H, br s); Found: C, 56.57; H, 4.86; N, 17.44%. $C_{11}H_{11}N_3O_3$ requires: C, 56.65; H, 4.75; N, 18.01%.

(*RS*)-1-(5-Methoxyindazol-3-yl)-2-propylamine fumarate

(*RS*)-1-(5-Methoxyindazol-3-yl)-2-propylamine fumarate was prepared according to the method described in Example 1 using 1-(5-methoxyindazol-3-yl)-2-nitropropene to give 0.030 g (40 %) of the product as an off-white solid: mp 171-173 °C; IR ν_{max}(Nujol)/cm^{-1} 1710, 1691, 1612, 1552 and 1504; NMR δ_H (400 MHz, DMSO-d_6) 1.15 (3H, d, *J* 6.5

Hz), 3.01 (1H, dd, *J* 8.3, 14.2 Hz), 3.20 (1H, dd, *J* 5.5, 14.4 Hz), 3.53 (1H, m), 3.79 (3H, s), 6.41 (1H, s), 6.99 (1H, dd, *J* 2.5, 9.0 Hz), 7.21 (1H, d, *J* 2.5 Hz) and 7.39 (1H, d, *J* 9.0 Hz).

Example 5: (*RS*)-1-(5-Methoxy-1-methylindazol-3-yl)-2-propylamine fumarate



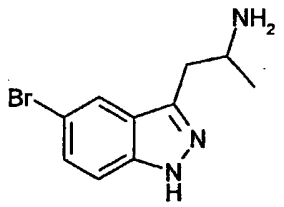
1-(5-Methoxy-1-methylindazol-3-yl)-2-nitropropene

1-(5-Methoxy-1-methylindazol-3-yl)-2-nitropropene was prepared according to the method described in Example 2 using 1-(5-methoxyindazol-3-yl)-2-nitropropene to give 0.48 g (55%) of the product as a yellow solid: mp 193-194 °C; IR ν_{max}(Nujol)/cm^{-1} 1650, 1511, 1315, 1287, 1243 and 1220; NMR δ_H (400 MHz, $CDCl_3$) 2.81 (3H, s), 3.91 (3H, s), 4.14 (3H, s), 7.12 (2H, m), 7.35 (1H, dd, *J* 1.5, 9.0 Hz) and 8.30 (1H, s); Found: C, 58.28; H, 5.30; N, 16.88%. $C_{12}H_{13}N_3O_3$ requires: C, 58.29; H, 5.30; N, 16.99%.

(*RS*)-1-(5-Methoxy-1-methylindazol-3-yl)-2-propylamine fumarate

(*RS*)-1-(5-Methoxy-1-methylindazol-3-yl)-2-propylamine fumarate was prepared according to the method described in Example 1 using 1-(5-methoxy-1-methylindazol-3-yl)-2-nitropropene to give 0.15 g (39%) of the product as an off-white solid: mp 135-136 °C; IR ν_{max}(Nujol)/cm^{-1} 1704, 1630, 1565, 1512, 1311, 1255 and 1221; NMR δ_H (400 MHz, DMSO-d_6) 1.17 (3H, d, *J* 6.6 Hz), 3.00 (1H, dd, *J* 8.7, 14.6 Hz), 3.21 (1H, dd, *J* 5.5, 14.7 Hz), 3.55 (1H, m), 3.78 (3H, s), 3.94 (3H, s), 6.43 (2H, s), 7.04 (1H, dd, *J* 2.0, 9.0 Hz), 7.21 (1H, d, *J* 2.0 Hz) and 7.49 (1H, d, *J* 9.0 Hz); Found: C, 53.88; H, 6.57; N, 11.91%. $C_{16}H_{21}N_3O_5.H_2O$ requires: C, 54.38; H, 6.56; N, 11.89%.

Example 6: (*RS*)-1-(5-Bromoindazol-3-yl)-2-propylamine fumarate



1-(5-Bromoindazol-3-yl)-2-nitropropene

1-(5-Bromoindazol-3-yl)-2-nitropropene was prepared according to the method described in Example 1 using 5-bromoindazole-3-carboxaldehyde (WO 9749698) to give 0.42 g (34%) of the product as a yellow solid: mp 219 °C; IR ν_{max}(Nujol)/cm^{-1} 3239, 1666, 1618, 1576, 1528, 1316, 1261 and 1243; NMR δ_H (400 MHz, DMSO-d_6) 2.74 (3H, s), 7.55 – 7.67 (2H, m), 8.40 (1H, d, *J* 1.0 Hz), 8.45 (1H, s) and 14.10 (1H, s); Found: C, 42.62; H, 2.89; N, 14.61%. $C_{10}H_8N_3O_2Br$ requires: C, 42.58; H, 2.86; N, 14.89%.

(*RS*)-5-Bromo-3-[(2-tert-butoxycarbonylamino)propyl]-indazole

To lithium aluminium hydride (0.18 g, 4.7 mmol) in anhydrous tetrahydrofuran (25 mL) was added dropwise 1-(5-bromoindazol-3-yl)-2-nitropropene (0.53 g, 1.88 mmol) in anhydrous tetrahydrofuran (5 mL). The reaction mixture was heated under reflux for 3 h. After cooling to room temperature, ether (25 mL) was added followed by sufficient saturated aqueous sodium sulfate solution to give a precipitate. The mixture was filtered through a pad of kieselguhr and the filtrate was concentrated *in vacuo* to yield an oil which was dissolved in dichloromethane (5 mL). To the stirred solution were added triethylamine (0.19 g, 1.91 mmol) and di-tert-butyl dicarbonate (0.38 g, 1.73 mmol). The reaction mixture was stirred for 16 h, concentrated *in vacuo* and purified by column chromatography [SiO_2; heptane-ethyl acetate (1 : 1)] to yield the product (0.28 g, 42%) as an off-white solid: mp 147-148 °C; IR ν_{max}(Nujol)/cm^{-1} 3368, 3268, 1684, 1648, 1620, 1526, 1253 and 1173; NMR δ_H (400 MHz, $CDCl_3$) 1.16 (3H, d, *J* 6.6 Hz), 1.42

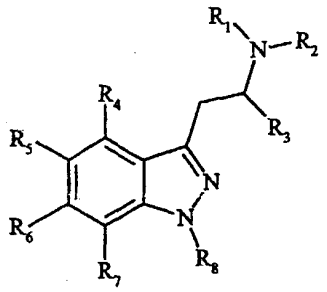
(9H, s), 3.12 (2H, dd, *J* 6.5, 14.0 Hz), 4.13 (1H, m), 4.77 (1H, br s), 7.44 (2H, m) and 7.87 (1H, m).

(*RS*)-1-(5-Bromoindazol-3-yl)-2-propylamine fumarate

A mixture of (*RS*)-5-bromo-3-[(2-tert-butoxycarbonylamino)propyl]-indazole (0.26 g, 0.73 mmol), dichloromethane (1 mL) and trifluoroacetic acid (5 mL) was stirred at 0 °C for 2 h, concentrated *in vacuo* and the partitioned between dichloromethane (20 mL) and saturated sodium bicarbonate solution (2 x 25 mL). The aqueous phase was basified to pH 10, extracted with dichloromethane (2 x 25 mL), washed with saturated brine (25 mL), dried (magnesium sulfate) and concentrated *in vacuo*. The concentrate was dissolved in ether (5 mL) and a solution of fumaric acid (0.041 g, 0.35 mmol) in 2-propanol (5 mL) was added. A precipitate formed which was dissolved in 2-propanol at 50 °C. The solution was cooled to 0 °C and filtered. The filter-cake was dried *in vacuo* to yield the product (0.12 g, 44%) as a white solid: mp 161 °C; IR ν_{max}(Nujol)/cm^{-1} 3147, 1674, 1638, 1548, 1508 1278 and 1213; NMR δ_H (400 MHz, DMSO-d_6) 1.19 (3H, d, *J* 6.5 Hz), 3.08 (1H, dd, *J* 8.0, 14.7 Hz), 3.25 (1H, dd, *J* 5.9, 14.5 Hz), 3.60 (1H, m), 6.50 (2H, s), 7.48 (2H, m) and 8.06 (1H, m).

CLAIMS

1. For use in therapy, a chemical compound of formula (I):



(I)

wherein:

R_1 and R_2 are independently selected from hydrogen and alkyl;

R_3 is alkyl;

R_4 to R_7 are independently selected from hydrogen, halogen, hydroxy, alkyl, aryl, amino, monoalkylamino, dialkylamino, alkoxy, aryloxy, alkylthio, arylthio, arylsulfoxyl, arysulfonyl, alkylsulfoxyl, alkylsulfonyl, nitro, cyano, carboxaldehyde, alkylcarbonyl, arylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkoxycarbonylamino, aminocarbonyloxy, monoalkylaminocarbonyloxy, dialkylaminocarbonyloxy, monoalkylaminocarbonylamino and dialkylaminocarbonylamino, wherein at least one of R_4 to R_7 is a substituent group other than hydrogen; and

R_8 is selected from hydrogen and alkyl,

and pharmaceutically acceptable salts and prodrugs thereof,

other than compounds in which R_1 is hydrogen and R_2 is $-CH_2CH(OH)$-Ar and other than compounds in which R_2 is H and R_1 is $-CH_2CH(OH)$-Ar wherein Ar is 3-halophenyl or 3-trifluoromethylphenyl.

2. A compound according to claim 1 wherein R_1 is the same as R_2.

3. A compound according to claim 1 wherein R_1 and R_2 are hydrogen.

4. A compound according to claim 1 wherein R_1 is hydrogen and R_2 is alkyl.

5. A compound according to claim 1, 2, 3 or 4 wherein R_3 is methyl.

6. A compound according to any of claims 1 to 5 wherein two or three of R_4, R_5, R_6 and R_7 are hydrogen.

7. A compound according to any one of claims 1 to 6 wherein one or both of R_4 and R_7 are hydrogen.

8. A compound according to any of claims 1 to 7 wherein one or both of R_5 and R_6 are selected from alkyl, alkoxy, alkylthio and halogen.

9. A compound according to any of claims 1 to 8 wherein R_8 is selected from hydrogen and methyl.

10. A compound according to claim 1 wherein the compounds of formula (I) are selected from 1-(5-chloroindazol-3-yl)-2-propylamine, 1-(5-chloro-1-methylindazol-3-yl)-2-propylamine, 1-(5-chloro-1-isopropylindazol-3-yl)-2-propylamine, 1-(5-methoxyindazol-3-yl)-2-propylamine, 1-(5-methoxy-1-methylindazol-3-yl)-2-propylamine and 1-(5-bromoindazol-3-yl)-2-propylamine.

11. A novel compound of formula (I) as set out in any one of claims 1 to 10, *per se*.

12. A compound of formula (I) according to claim 11 wherein at least one of R_4 to R_8 is a substituent other than methyl.

13. A compound of formula (I) according to claim 11 wherein at least one of R_4 to R_7 is a substituent other than chloro or methoxy.

14. The use of a compound of formula (I) as set out in any of claims 1 to 10 in the manufacture of a medicament for the treatment of disorders of the central

nervous system; damage to the central nervous system; cardiovascular disorders; gastrointestinal disorders; diabetes insipidus, and sleep apnea.

15. A use according to claim 14 wherein the disorders of the central nervous system are selected from depression, atypical depression, bipolar disorders, anxiety disorders, obsessive-compulsive disorders, social phobias or panic states, sleep disorders, sexual dysfunction, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or other pain, raised intracranial pressure, epilepsy, personality disorders, age-related behavioural disorders, behavioural disorders associated with dementia, organic mental disorders, mental disorders in childhood, aggressivity, age-related memory disorders, chronic fatigue syndrome, drug and alcohol addiction, obesity, bulimia, anorexia nervosa and premenstrual tension.

16. A use according to claim 14 wherein the damage to the central nervous system is by trauma, stroke, neurodegenerative diseases or toxic or infective CNS diseases.

17. A use according to claim 16 wherein said toxic or infective CNS disease is encephalitis or meningitis

18. A use according to claim 16 wherein the cardiovascular disorder is thrombosis.

19. A use according to claim 14 wherein the gastrointestinal disorder is dysfunction of gastrointestinal motility

20. A use according to claim 14 wherein said medicament is for the treatment of obesity.

21. A use according to any one of claims 14 to 20 wherein said treatment is prophylactic treatment.

22. A method of treatment of any of the disorders set out in claims 14 to 19 comprising administering to a patient in need of such treatment an effective dose of a compound of formula (I) as set out in any one of claims 1 to 10.

23. A method of treatment according to claim 22 wherein said disorder is obesity.

24. A method according to claim 22 or 23 wherein said treatment is prophylactic treatment.

25. A method of preparing a compound of formula (I) as set out in any one of claims 1 to 10.

26. A pharmaceutical composition comprising a compound of formula (I) as set out in any one of claims 1 to 10 in combination with a pharmaceutically acceptable carrier or excipient.

27. A method of making a composition according to claim 26 comprising combining a compound of formula (I) as set out in any one of claims 1 to 10 with a pharmaceutically acceptable carrier or excipient.

INTERNATIONAL SEARCH REPORT

Intern nal Application No
PCT/GB 99/02883

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D231/56 A61K31/416 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US CARNMALM, BERNT ET AL: "Antidepressant agents. III. Aza analogs of etryptamine" retrieved from STN Database accession no. 81:37512 XP002133733 compound with RN=53374-75-7 abstract & ACTA PHARM. SUEC. (1974), 11(2), 196-200 ,	1-3,6,7, 11,25-27

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 March 2000	03/04/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	De Jong, B

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB 99/02883

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US KATO, SHIRO ET AL: "Preparation of 2-alkylamino-1-phenylethanol derivatives as.beta.3-adrenergic agents" retrieved from STN Database accession no. 125:195419 XP002133734 abstract -& JP 08 165276 A (DAINIPPON PHARMACEUTICAL CO, JAPAN) 25 June 1996 (1996-06-25) cited in the application page 21 -page 22	1,10
A	EP 0 494 774 A (MERCK SHARP & DOHME) 15 July 1992 (1992-07-15) cited in the application examples	1,10, 25-27
A	WO 98 30548 A (TSUKAMOTO SHIN ICHI ;KUBOTA HIDEKI (JP); MAENO KYOICHI (JP); SHIMA) 16 July 1998 (1998-07-16) cited in the application abstract	1,10, 25-27

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INTERNATIONAL SEARCH REPORT

Ir.. .national application No.
PCT/GB 99/02883

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 22-24
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 22-24 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter xnal Application No
PCT/GB 99/02883

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 8165276 A	25-06-1996	NONE	
EP 0494774 A	15-07-1992	CA 2058805 A	12-07-1992
		JP 2539127 B	02-10-1996
		JP 5039290 A	19-02-1993
		US 5208248 A	04-05-1993
WO 9830548 A	16-07-1998	AU 5343298 A	03-08-1998